Multhoff 10/ 526 586 = Granzyme B & Hsp70 NK cells vs. Cancer

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LOGINID:SSPTAHPY1654

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FILE 'HOME' ENTERED AT 10:13:03 ON 26 FEB 2007

=> file biosis embase medline
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
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FULL ESTIMATED COST                                       0.21       0.21

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FILE 'MEDLINE' ENTERED AT 10:13:19 ON 26 FEB 2007

=> s gabriele multhodd
L1             0 GABRIELE MULTHODD

=> s gabriele multhoff
L2             2 GABRIELE MULTHOFF

=> d L2 1-2 bib abs

L2   ANSWER 1 OF 2  BIOSIS  COPYRIGHT (c) 2007 The Thomson Corporation  on STN
AN   2005:227233  BIOSIS
DN   PREV200510011552
TI   Introducing Professor Gabriele Multhoff, European
     Regional Editor.
AU   Hightower, Lawrence E.
SO   Cell Stress & Chaperones, (SPR 2005) Vol. 10, No. 1, pp. 2-3.
     ISSN: 1355-8145.
DT   Letter
     Editorial
LA   English
ED   Entered STN: 16 Jun 2005
     Last Updated on STN: 16 Jun 2005

L2   ANSWER 2 OF 2  EMBASE  COPYRIGHT (c) 2007 Elsevier B.V. All rights
     reserved on STN
AN   2005147399  EMBASE
TI   Introducing Professor Gabriele Multhoff, European
     Regional Editor.
AU   Hightower L.E.
SO   Cell Stress and Chaperones, (2005) Vol. 10, No. 1, pp. 2-3. .
     Refs: 11
     ISSN: 1355-8145  CODEN: CSCHFG
CY   United States
DT   Journal; Editorial
FS   017     Public Health, Social Medicine and Epidemiology
LA   English
ED   Entered STN: 21 Apr 2005
     Last Updated on STN: 21 Apr 2005
       DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER
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=> s granzyme(P)administer
L3            0 GRANZYME(P) ADMINISTER

=> s granzyme(P)treatment
L4          622 GRANZYME(P) TREATMENT

=> s L4 and cancer
L5          125 L4 AND CANCER

=> s L5 and Hsp70
L6            2 L5 AND HSP70

=> d L6 bib abs

L6   ANSWER 1 OF 2  EMBASE  COPYRIGHT (c) 2007 Elsevier B.V. All rights
     reserved on STN
AN   2004233364  EMBASE
TI   Differential up-regulation of cytosolic and membrane-bound heat shock
     protein 70 in tumor cells by anti-inflammatory drugs.
AU   Gehrmann M.; Brunner M.; Pfister K.; Reichle A.; Kremmer E.; Multhoff G.
CS   G. Multhoff, Dept. of Hematology and Oncology, University Hospital
     Regensburg, Franz-Josef-Strauss Allee 11, 93053 Regensburg, Germany.
     gabriele.multhoff@klinik.uni-regensburg.de
SO   Clinical Cancer Research, (15 May 2004) Vol. 10, No. 10, pp. 3354-3364.
     Refs: 40
     ISSN: 1078-0432  CODEN: CCREF4
CY   United States
DT   Journal; Article
FS   016     Cancer
     030     Pharmacology
     037     Drug Literature Index
LA   English
SL   English
ED   Entered STN: 28 Jun 2004
     Last Updated on STN: 28 Jun 2004
AB   Purpose: Modulation of the heat shock protein (HSP) response affects
     sensitivity to therapeutic agents in cancer.  Here, drugs with
     anti-inflammatory potential (cyclooxygenase 1/2 inhibitors) and peroxidase
     proliferator-activated receptor-.gamma. agonists were analyzed for their
     capacity to affect Hsp70 expression in human cancer
     cells with a divergent Hsp70 membrane expression pattern.
     Experimental Design: In dose kinetics, the nonlethal concentration of
     acetyl-salicyl acid, celecoxib, rofecoxib, and the insulin-sensitizer
     pioglitazone was identified for the human adenocarcinoma cell line CX-.
     With the exception of CLX, which was diluted in DMSO, all reagents were
     dissolved in water.  After treatment with the different
     compounds at nontoxic concentrations for 6 h, followed by a 1-h recovery
     period, the cytosolic Hsp70 levels were measured in CX-2 and CX-
     tumor cells by Western blot analysis.  Fold increase was calculated in
     relation to the housekeeping protein tubulin.  Membrane-bound
     Hsp70 was analyzed by flow cytometry using a FITC-labeled
     Hsp70-specific monoclonal antibody.  Untreated cells and cells
     incubated with equivalent amounts of the diluting agents served as
     controls.  The immunological function was tested in granzyme B
     apoptosis assays, standard (51)Cr release assays, and antibody blocking
     studies.  Results: Compared with aqua dest, the cytoplasmic amount of
     Hsp70 was equally enhanced in CX-2 and CX-cells by all compounds.
     An increase in membrane-bound Hsp70,. detected selectively in CX-
     cells, corresponded to an enhanced sensitivity to granzyme B-
     and natural killer cell-mediated kill that was blockable by using a
     Hsp70-specific antibody.  Conclusions: Although increase in
     cytosolic Hsp70 levels conferred resistance to further stress,
     membrane-bound Hsp70 rendered tumor cells more sensitive to the
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immunological attack mediated by granzyme B and natural killer cells. Our data provide a biological rational for combining anti-inflammatory drugs with immunotherapy in cancer therapy.

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=> s L5 and granzyme(L)dose
L7          15 L5 AND GRANZYME(L) DOSE

=> dup rem L7
PROCESSING COMPLETED FOR L7
L8          10 DUP REM L7 (5 DUPLICATES REMOVED)

=> d L8 1-5 bib abs

L8   ANSWER 1 OF 10  EMBASE  COPYRIGHT (c) 2007 Elsevier B.V. All rights
     reserved on STN
AN   2007018583  EMBASE
TI   Impact of interferon-.alpha. in combined chemoradioimmunotherapy for
     pancreatic adenocarcinoma (CapRI): First data from the immunomonitoring.
AU   Schmidt J.; Jager D.; Hoffmann K.; Buchler M.W.; Marten A.
CS   Dr. A. Marten, Department of Surgery, Im Neuenheimer Feld 350, 69120
     Heidelberg, Germany. angela.maerten@med.uni-heidelberg.de
SO   Journal of Immunotherapy, (2007) Vol. 30, No. 1, pp. 108-115. .
     Refs: 32
     ISSN: 1524-9557  CODEN: JOIME7
PUI  000023712007010000011
CY   United States
DT   Journal; Article
FS   016     Cancer
     026     Immunology, Serology and Transplantation
     030     Pharmacology
     037     Drug Literature Index
     048     Gastroenterology
LA   English
SL   English
ED   Entered STN: 5 Feb 2007
     Last Updated on STN: 5 Feb 2007
AB   Data from a phase II trial combining chemoradiotherapy with IFN-.alpha.
     (CapRI scheme) for adjuvant treatment of pancreatic carcinoma
     are very encouraging. Therefore, a phase III trial comparing chemotherapy
     with the chemoradiotherapy with IFN-.alpha. scheme has been initiated in
     August 2004. Translational research with a focus on immunomodulation is
     performed in parallel to the study. Blood and serum samples are taken at
     various time points. Patients in arm A (chemoradioimmunotherapy) receive
     a single low-dose-Interferon injection before therapy to
     investigate the direct effect of IFN-.alpha.. So far samples from 44
     patients have been investigated for surface molecule expression, cytokine
     levels, natural killer cell cytotoxicity, and antigen-specific
     Granzyme B release. Patients in arm A showed 1 day after
     IFN-.alpha. injection a significant increase in spontaneous cytotoxicity;
     this effect was fading after repeated injections. Furthermore, cells
     releasing Granzyme B after stimulation with CA 19.9 and MUC-1
     protein increased under therapy. Five days after the first IFN-.alpha.
     injection, IL-12 and TNF-.alpha. serum levels peak. We observed
     significant increases of monocytes, peripheral dendritic cells, CD40
     cells, central and effector memory T cells, and CD8 cells, CD4 cells
     decreased during therapy. All these effects were only observed in arm A
     patients and none of them in arm B patients. In conclusion, in a
     translational research project accompanying a challenging multimodality
     treatment trial including IFN-.alpha., we observed an immediate
     activation of antigen-presenting cells and natural killer cells followed
     later on by antigen-specific activation. It will be most interesting if
     the immunologic data will show a correlation with the clinical course of
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the patients. .COPYRGT. 2007 Lippincott Williams & Wilkins, Inc.

L8 ANSWER 2 OF 10 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
DUPLICATE 1
AN 2006:332682 BIOSIS
DN PREV200600326054
TI Proteomic analysis and the antimetastatic effect of N-(4-methyl)phenyl-O-(4-methoxy) phenyl-thionocarbamate-induced apoptosis in-human melanoma SK-MEL-28 cells.
AU Choi, Su-La; Choi, Yun-Sil; Kim, Young-Kwan; Sung, Nack-Do; Kho, Chang-Won; Park, Byong-Chul; Kim, Eun-Mi; Lee, Jung-Hyung; Kim, Kyung-Mee; Kim, Min-Yung; Myung, Pyung-Keun [Reprint Author]
CS Chungnam Natl Univ, Coll Pharm, Dept Pharm, Clin Biochem Lab, Taejon 305764, South Korea
pyung@cnu.ac.kr
SO Archives of Pharmacal Research (Seoul), (MAR 2006) Vol. 29, No. 3, pp. 224-234.
CODEN: APHRDQ. ISSN: 0253-6269.
DT Article
LA English
ED Entered STN: 28 Jun 2006
Last Updated on STN: 28 Jun 2006
AB We employed human SK-MEL-28 cells as a model system to identify cellular proteins that accompany N-(4-methyl)phenyl-O-(4-methoxy)phenyl-thionocarbamate (MMTC)-induced apoptosis based on a proteomic approach. Cell viability tests revealed that SK-MEL-28 skin cancer cells underwent more cell death than normal HaCaT cells in a dose -dependent manner after treatment with MMTC. Two-dimensional electrophoresis in conjunction with matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry analysis or computer matching with a protein database further revealed that the MMTC-induced apoptosis is accompanied by increased levels of caspase-1, checkpoint suppressor-1, caspase-4, NF-kappa B inhibitor, AP-2, c-Jun-N-terminal kinase, melanoma inhibitor, granzyme K, G1/S specific cyclin D3, cystein rich protein, Ras-related protein Rab-37 or Ras-related protein Rab-13, and reduced levels of EMS (oncogene), ATP synthase, tyrosine-phosphatase, Cdc25c, 14-3-3 protein or specific structure of nuclear receptor. The migration suppressing effect of MMTC; on SK-MEL-28 cell was tested. MMTC suppressed the metastasis of SK-MEL-8 cells. It was also identified that MMTC had little angiogenic effect because it did not suppress the proliferation of HUVEC cell line. These results suggest that MMTC is a novel chemotherapeutic and metastatic agents against the SK-MEL-28 human melanoma cell line.

L8 ANSWER 3 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2006217238 EMBASE
TI Targeted apoptosis activation with GrB/scFvMEL modulates melanoma growth, metastatic spread, chemosensitivity, and radiosensitivity.
AU Liu Y.; Zhang W.; Niu T.; Cheung L.H.; Munshi A.; Meyn Jr. R.E.; Rosenblum M.G.
CS Dr. M.G. Rosenblum, Department of Experimental Therapeutics, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030, United States. mrosenbl@mdanderson.org
SO Neoplasia, (2006) Vol. 8, No. 2, pp. 125-135. .
Refs: 54
ISSN: 1522-8002 E-ISSN: 1476-5586 CODEN: NEOPFL
CY United States
DT Journal; Article
FS 013 Dermatology and Venereology
014 Radiology
016 Cancer
029 Clinical Biochemistry

037 Drug Literature Index
LA English
SL English
ED Entered STN: 30 May 2006
Last Updated on STN: 30 May 2006
AB GrB/scFvMEL, a fusion protein composed of human granzyme B (GrB) and the single-chain antibody scFvMEL, targets melanoma gp240 antigen and exerts impressive cytotoxic effects by inducing apoptosis. We evaluated the effects of GrB/scFvMEL on chemotherapy, radiation therapy, metastasis in vitro, and the growth of human melanoma A375 xenograft tumors in nude mice. GrB/scFvMEL showed synergistic cytotoxicity when coadministered with doxorubicin, vincristine or cisplatin, and additive effects, in combination with etoposide or cytarabine. Optimal cytotoxic effects were obtained when cells were treated first with GrB/scFvMEL followed by exposure to the agent (rather than the reverse). Pretreatment of A375 cells with GrB/scFvMEL significantly sensitized melanoma cells to ionizing radiation assessed using a clonogenic survival assay. Subtoxic doses of GrB/scFvMEL inhibited the invasion of A375 cells into Matrigel. GrB/scFvMEL (37.5 mg/kg) was administered intravenously to nude mice bearing A375 tumors. Saline-treated tumors increased 24-fold, whereas tumors treated with GrB/scFvMEL showed a significant tumor growth delay increasing four-fold. Tumor tissue displayed an increase in apoptotic nuclei compared to control. Thus, the targeted delivery of GrB to tumors may have a significant potential for cancer treatment.
Targeted therapeutic agents specifically designed to impact cellular apoptotic pathways may represent a novel class of therapeutic agents.
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L8 ANSWER 4 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2005310709 EMBASE
TI Destructive facial T-cell lymphoma: The difficulty in diagnosis of pyoderma-like processes.
AU Gibson L.E.; Hairston B.R.; Belt R.J.; el-Azhary R.
CS Dr. R. el-Azhary, Department of Dermatology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, United States. elazhary.rokea2@mayo.edu
SO International Journal of Dermatology, (2005) Vol. 44, No. 7, pp. 579-583.
.
Refs: 26
ISSN: 0011-9059 CODEN: IJDEBB
CY United Kingdom
DT Journal; Article
FS 013 Dermatology and Venereology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
016 Cancer
025 Hematology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
ED Entered STN: 5 Aug 2005
Last Updated on STN: 5 Aug 2005
AB A 48-year-old woman presented with extensive facial ulceration of 1 year in duration. Based on the combination of the clinical appearance and a "nondiagnostic" biopsy taken elsewhere, the patient was started on oral prednisone at a dose of 40 mg/day, with a working diagnosis of pyoderma gangrenosum. According to the patient, the ulceration worsened over the 2 months whilst on prednisone and pain control was a major issue, controlled for the most part with oral oxycodone. One month prior to our evaluation of the patient, she was started on dapsone at 50 mg/day with no added benefit. Approximately 2 years prior to our evaluation, she developed raised, reddish, skin lesions on the abdomen and legs which recurred, but healed spontaneously each time after a few weeks. Her past

medical history was remarkable for the remote use of intravenous drugs (which she had stopped for the past 20 years) and the past and continued use of alcohol on a daily basis. She had recently been tested elsewhere and was found to be positive for hepatitis C, but not human immunodeficiency virus (HIV). Examination revealed several ulcerations of the face and forehead, with an "apple jelly" coloration to the periphery and necrotic center. There was complete erosion of the nasal sidewall with apparent involvement of the septum (Fig. 1). There were also scattered, smaller, nonulcerated, reddish to purplish lesions on the abdomen. Otolaryngologic examination revealed ulceration of the right ala and erosion of the nasal septum, but was otherwise unremarkable. No cervical or submental lymphadenopathy was noted. Routine laboratory tests showed the patient to be anemic, with a hemoglobin level of 11 g/dL (normal, 12-15.5 g/dL) and a white blood count of 13,300 (normal, 3500-10,500) The total bilirubin was normal at 1.0 mg/dL, but several liver function tests were elevated by 2-4 times the upper limit of normal, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and .gamma.-glutamyl transpeptidase (G-GT). Hepatitis C tests were abnormal, including antibody to hepatitis B core antigen (anti-HBc) and anti-hepatitis C virus (anti-HCV) antibodies, and hepatitis C-RNA was positive. Anti-hepatitis B surface antigen (anti-HBsAg) and antibody were negative. Human immunodeficiency virus (HIV) was negative. Antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), serologic tests for syphilis, cryoglobulins and cryofibrinogens, renal function, and urinalysis were all either negative or normal. The chest X-ray showed bilateral pulmonary nodules, confirmed by computed tomography (CT) scan of the chest. Serologic tests for several fungal organisms, including Sporothrix and Cryptococcus, were negative. Tuberculin skin testing was negative. Two 4-mm punch biopsies were taken from the right cheek and from the right lower lateral abdomen near the hip. Biopsy of facial tissue cultures for acid-fast bacilli and fungal elements was negative. Bacterial culture revealed 1+ Staphylococcus aureus and coagulase-negative Staphylococcus. Polymerase chain reaction (PCR) testing for herpes and varicella viruses was negative. Histologic examination of the skin biopsies revealed identical findings from both sites. There was parakeratosis, serum crust, and mild irregular epidermal acanthosis. Focal interfacial dermatitis was present and characterized by basal vacuolization and melanophages in the superficial dermis. Epidermotropism of atypical lymphocytes singly and in cell clusters was seen in the epidermis. In the papillary and reticular dermis, extending to the subcutaneous fat, there was a dense, diffuse, perivascular, interstitial, and periappendageal infiltrate composed of atypical lymphocytes, lymphocytes, histiocytes, plasma cells, and neutrophils. The atypical lymphocytes infiltrated the hair follicles with little associated spongiosis (pilotropism) (Fig. 2). The atypical lymphocytes also surrounded and infiltrated the eccrine glands and blood vessels. Immunoperoxidase studies were performed on paraffin tissue and showed that the atypical lymphocytes were immunoreactive with CD3 (Fig. 3) and .beta.F1, but not with CD8, CD56, T-cell-restricted intracellular antigen-1 (TIA-1), or granzyme B. There was a reactive population of B lymphocytes immunoreactive with CD20. In situ hybridization for Epstein-Barr virus (EBV), performed on paraffin sections, was negative. Lung biopsy of several nodules was accomplished via video-assisted thoracoscopy and revealed a peripheral T-cell lymphoma. Gene rearrangement studies of skin and lung nodules showed similar T-cell clones and were positive for T-cell rearrangement by PCR (TCR PCR, T .gamma.-chain positive). The final diagnosis was peripheral T-cell lymphoma with pulmonary and skin involvement. There was no evidence for EBV infection. The patient returned home to receive treatment with four cycles of hyper-CVAD (cyclophosphamide, vincristine, adriamycin, and dexamethasone), followed by autologous stem cell transplantation. The facial erosions and ulcerations, as well as the systemic nodules, responded well to therapy, with only limited recurrence of the right lower

lateral abdominal lesions, which were subsequently treated with radiation (Fig. 4). The patient's clinical status 18 months after treatment is complete remission from lymphoma, but she has developed fulminant liver failure secondary to cirrhosis associated with hepatitis C. .COPYRGT. 2004 The International Society of Dermatology.

L8 ANSWER 5 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 2
AN 2004233364 EMBASE
TI Differential up-regulation of cytosolic and membrane-bound heat shock protein 70 in tumor cells by anti-inflammatory drugs.
AU Gehrmann M.; Brunner M.; Pfister K.; Reichle A.; Kremmer E.; Multhoff G.
CS G. Multhoff, Dept. of Hematology and Oncology, University Hospital Regensburg, Franz-Josef-Strauss Allee 11, 93053 Regensburg, Germany. gabriele.multhoff@klinik.uni-regensburg.de
SO Clinical Cancer Research, (15 May 2004) Vol. 10, No. 10, pp. 3354-3364. . Refs: 40
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
ED Entered STN: 28 Jun 2004
Last Updated on STN: 28 Jun 2004
AB Purpose: Modulation of the heat shock protein (HSP) response affects sensitivity to therapeutic agents in cancer. Here, drugs with anti-inflammatory potential (cyclooxygenase 1/2 inhibitors) and peroxidase proliferator-activated receptor-.gamma. agonists were analyzed for their capacity to affect Hsp70 expression in human cancer cells with a divergent Hsp70 membrane expression pattern. Experimental Design: In dose kinetics, the nonlethal concentration of acetyl-salicyl acid, celecoxib, rofecoxib, and the insulin-sensitizer pioglitazone was identified for the human adenocarcinoma cell line CX-. With the exception of CLX, which was diluted in DMSO, all reagents were dissolved in water. After treatment with the different compounds at nontoxic concentrations for 6 h, followed by a 1-h recovery period, the cytosolic Hsp70 levels were measured in CX-2 and CX- tumor cells by Western blot analysis. Fold increase was calculated in relation to the housekeeping protein tubulin. Membrane-bound Hsp70 was analyzed by flow cytometry using a FITC-labeled Hsp70-specific monoclonal antibody. Untreated cells and cells incubated with equivalent amounts of the diluting agents served as controls. The immunological function was tested in granzyme B apoptosis assays, standard (51)Cr release assays, and antibody blocking studies. Results: Compared with aqua dest, the cytoplasmic amount of Hsp70 was equally enhanced in CX-2 and CX-cells by all compounds. An increase in membrane-bound Hsp70, detected selectively in CX- cells, corresponded to an enhanced sensitivity to granzyme B- and natural killer cell-mediated kill that was blockable by using a Hsp70-specific antibody. Conclusions: Although increase in cytosolic Hsp70 levels conferred resistance to further stress, membrane-bound Hsp70 rendered tumor cells more sensitive to the immunological attack mediated by granzyme B and natural killer cells. Our data provide a biological rational for combining anti-inflammatory drugs with immunotherapy in cancer therapy.

=> d L8 6-10 bib abs

L8 ANSWER 6 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AN 2004327345 EMBASE
TI Primary omental gamma/delta T-cell lymphoma involving the central nervous system.
AU Harada Y.; Kato S.; Komiya H.; Shirota T.; Mukai K.; Hayashi T.
CS Y. Harada, The Third Dept. of Internal Medicine, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan. yharada@tokyo-med.ac.jp
SO Leukemia and Lymphoma, (2004) Vol. 45, No. 9, pp. 1947-1950. .
Refs: 14
ISSN: 1042-8194 CODEN: LELYEA
CY United Kingdom
DT Journal; Article
FS 008 Neurology and Neurosurgery
016 Cancer
025 Hematology
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
ED Entered STN: 19 Aug 2004
Last Updated on STN: 19 Aug 2004
AB Gamma/delta T-cell lymphoma (GDTL) is an uncommon lymphoma that was initially reported to involve only the liver and spleen. GDTL other than the hepatosplenic type is extremely rare. Frequent primary sites include skin and subcutaneous tissue, intestine, or nasal region. We report a case of GDTL of the omentum in a 54 year-old-man. The tumor cells are CD2(-), CD3(+), CD4(-), CD5(-), CD8(+), CD56(+), TIA-1(+), granzyme B(.+-.). They expressed the identical phenotype of intestinal GDTL. The patient was treated with 2 courses of CHOP which comprised cyclophosphamide, doxorubicin, vincristine and prednisolone, and 3 courses of EPOCH which comprised etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin. However, he failed to obtain remission. During the fourth course of EPOCH, muscle weakness of the lower extremities developed and intracranial masses were observed by computed tomographic scan of the brain. Dissemination of lymphoma to the central nervous system was considered and it may be attributable to the expression of CD56 in this case. High dose methotrexate (HD-MTX) chemotherapy successfully eliminated the omental tumor and reduced the size of the intracranial masses, thus HD-MTX appears to be an effective treatment against GDTL. .COPYRGT. 2004 Taylor & Francis Ltd.

L8 ANSWER 7 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN
AN 2003498587 EMBASE
TI Hepatosplenic .gamma..delta. T-cell lymphoma is a rare clinicopathologic entity with poor outcome: Report on a series of 21 patients.
AU Belhadj K.; Reyes F.; Farcet J.-P.; Tilly H.; Bastard C.; Angonin R.; Deconinck E.; Charlotte F.; Leblond V.; Labouyrie E.; Lederlin P.; Emile J.-F.; Delmas-Marsalet B.; Arnulf B.; Zafrani E.-S.; Gaulard P.
CS P. Gaulard, Departement de Pathologie and EA2348, CHU Henri Mondor, 94010, Creteil, France. philippe.gaulard@hmn.ap-hop-paris.fr
SO Blood, (15 Dec 2003) Vol. 102, No. 13, pp. 4261-4269. .
Refs: 82
ISSN: 0006-4971 CODEN: BLOOAW
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
048 Gastroenterology
LA English
SL English

ED Entered STN: 16 Jan 2004
Last Updated on STN: 16 Jan 2004

AB We report on the characteristics of 21 patients with hepatosplenic .gamma..delta. T-cell lymphoma (HS.gamma..delta.TCL), an entity recognized since 1994 in the Revised European American Lymphoma (REAL) classification. Median age was 34 years. Patients had splenomegaly (n = 21), hepatomegaly (n = 15), and thrombocytopenia (n = 20). Histopathologic findings were homogeneous and showed the presence of medium-sized lymphoma cells within the sinusoids of splenic red pulp, liver, and bone marrow. Marrow involvement was usually mild but could be demonstrated by phenotyping in all patients. Cells were CD3 (+)CD5(-), expressed the .gamma..delta. T-cell receptor, and had a nonactivated cytotoxic cell phenotype (TIA-1(+), granzyme B (-)). Most patients were CD4(-)/CD8(-) (16 of 18); CD56(+) (15 of 18), expressed the V.delta.1epitope (Vd1 (+)/Vd2(-)/Vd3(-)) (9 of 12); and were negative for Epstein-Barr virus (EBV) (18 of 20). Isochromosome arm 7q was documented in 9 of 13 patients. Eight patients had previously undergone kidney transplantation or had a history of systemic lupus, Hodgkin disease, or malaria. Prognosis was poor; median survival time was 16 months, and all but 2 patients ultimately died despite consolidative or salvage high-dose therapy. In conclusion, HS.gamma..delta.TCL is a disease with distinctive clinical, histopathologic, and phenotypic characteristics. Bone marrow biopsy with combined phenotyping is sufficient for diagnosis, and splenectomy is therefore unwarranted. Current treatment modalities appear to be ineffective in most patients. .COPYRGT. 2003 by The American Society of Hematology.

L8 ANSWER 8 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

AN 2003239700 EMBASE

TI Successful treatment of a patient with subcutaneous panniculitis-like T-cell lymphoma with high-dose chemotherapy and total body irradiation.

AU Mukai H.Y.; Okoshi Y.; Shimizu S.; Katsura Y.; Takei N.; Hasegawa Y.; Kojima H.; Mori N.; Nagasawa T.

CS Dr. H.Y. Mukai, Division of Hematology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki, 305-8575, Japan. hmukai@md.tsukuba.ac.jp

SO European Journal of Haematology, (1 Jun 2003) Vol. 70, No. 6, pp. 413-416.
.
Refs: 9
ISSN: 0902-4441 CODEN: EJHAEC

CY United Kingdom

DT Journal; Article

FS 025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index

LA English

SL English

ED Entered STN: 3 Jul 2003
Last Updated on STN: 3 Jul 2003

AB A 24-yr-old man was referred for fever, right cheek swelling, subcutaneous tumor and liver dysfunction. Physical examination showed an elastic hard subcutaneous tumor on the right cheek, left axillary lymph node swelling and multiple small subcutaneous tumors in the trunk. Laboratory examinations showed elevated levels of transaminase, soluble interleukin-2 receptor and ferritin. Biopsy of the subcutaneous tumor showed proliferation of medium-sized cells with abundant clear cytoplasm and hyperchromatic nuclei among the subcutaneous fat tissues. These cells showed CD3(+), CD4(-), CD8(+), CD56(-) and CD20(-) phenotype and possessed cytotoxic molecules such as granzyme B and T-cell intracellular antigen-1. Bone marrow aspiration showed proliferation of small numbers of abnormal lymphocytes with severe hemophagocytosis. He was thus diagnosed as having subcutaneous panniculitis-like T-cell lymphoma (SPTCL)

and treated with dose-escalated CHOP regimen. After three courses of the chemotherapy, he was further treated with high-dose chemotherapy and total body irradiation (TBI) with autologous peripheral blood stem cell rescue. Thereafter, he has been in remission for more than 2 yr. We consider that SPTCL with hemophagocytosis is an extremely aggressive disease, and high-dose chemotherapy and TBI should be included for the choice of the treatment.

L8 ANSWER 9 OF 10 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN DUPLICATE 3
AN 1999234449 EMBASE
TI Treatment of post-transfusion graft-versus-host disease with nafmostat mesilate, a serine protease inhibitor.
AU Ryo R.; Saigo K.; Hashimoto M.; Kohsaki M.; Yasufuku M.; Watanabe N.; Okada M.; Tadokoro K.; Juji T.
CS Dr. R. Ryo, Division of Blood Transfusion, Kobe University Hospital, Chuo, Kobe 650, Japan. ryo@med.kobe-u.ac.jp
SO Vox Sanguinis, (1999) Vol. 76, No. 4, pp. 241-246. .
Refs: 27
ISSN: 0042-9007 CODEN: VOSAAD
CY Switzerland
DT Journal; Article
FS 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
ED Entered STN: 27 Jul 1999
Last Updated on STN: 27 Jul 1999
AB Background: Cytotoxic T lymphocytes from donors are thought to injure the target organs in post-transfusion graft-versus-host disease (PT-GVHD) through perforin-granzyme- and Fas-dependent cell killings. The protease involved is a serine protease, and nafmostat mesilate (NM), a serine protease inhibitor, has been found to inhibit the in vitro allocytotoxicity of the T cell clone established from a patient with PT-GVHD, thus suggesting the usefulness of NM for treatment of PT-GVHD. Case Report: A 47-year-old male with esophageal cancer , who received 3 units of packed red cells and 20 units of platelet concentrates from 5 unrelated donors, was diagnosed as having PT-GVHD on the basis of typical clinical features, HLA typing of the patient and the responsible donor, and a mixed chimera of CD8+ lymphocytes on microsatellite DNA polymorphism analysis. NM was administered to inhibit the activity of the serine proteases, thought to be granzymes; a liver dysfunction and thrombocytopenia with leukocytopenia simultaneously improved. Subsequently, a high-dose methylprednisolone pulse therapy and monoclonal anti-CD3 were administered to reduce the donor's proliferating lymphocytes, which resulted in lymphopenia accompanied by elimination of the donor's lymphocytes and normalization of the CD4/CD8 ratio. However, recurrence of the proliferation of the responsible donor's lymphocytes developed after cessation of NM administration, probably because of excessive immunosuppression caused by steroids and the monoclonal anti-CD3. Conclusion: This case indicates that administration of a serine protease inhibitor may improve PT-GVHD symptoms by inhibiting cytotoxic T-cell-mediated killing of target cells in fatal PT-GVHD. Steroids and monoclonal anti-CD3 were probably responsible for the transient clinical improvements. More studies are required, however, on mechanisms to eliminate the donor's lymphocytes.

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TI The lack of NK cytotoxicity associated with fresh HUCB may be due to the presence of soluble HLA in the serum.

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DT Article

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AB Human bone marrow transplantation is becoming more common in the treatment of certain forms of cancer despite the scarcity of HLA matched donors. Because human umbilical cord blood (HUCB) has been used as a source for stem cells in bone marrow transplantation, and because NK cells appear to be important in graft versus leukemia response, we investigated the lytic activity of freshly isolated HUCB NK cells (HUCB-NK) against tumor targets and their ability to differentiate into LAK cells following stimulation with various cytokines. Although cytotoxicity mediated by fresh HUCB-NK was low compared to that of adult peripheral blood lymphocyte-derived NK cells (PBL-NK), the ability of HUCB-NK to bind to K562 target cells (TC) was similar to PBL-NK. In addition, the PBL-NK cytotoxicity of postpartum mothers was also low compared to that of normal adult PBL-NK. When we incubated HUCB for 18 hr in either IL-2 or IL- 12, we boosted the level of HUCB-NK cytotoxicity to approximately the level observed in PBL-NK and increased the level of perforin, granzyme A, and granzyme B mRNA expression.
In addition, when we incubated HUCB in IL-2, IL-4, IL-7, IL-12, TNF-alpha, IFN-alpha, IFN-gamma, or TGF-beta for 5 days, we observed that HUCB was capable of generating LAK cells only when incubated with either IL-2 or IL-12. In contrast. IL-2, IL-7, IL-12, TNF-alpha, and IFN-gamma all generated LAK cells from adult PBL. When we added to the medium low-dose IL-2 and irradiated K562 as feeder cells (mini-LAK), we were unable to generate LAK activity from HUCB-NK, whereas we could generate it with PBL-NK cells under the same conditions. Addition of serum derived from HUCB in a 4-hr 51Cr release assay with PBL-NK as the effector cells (EC) and K562 as the TC resulted in a 42% decrease in PBL-NK-mediated cytotoxicity. Although we detected no TGF-beta in HUCB serum, we did detect high concentrations of soluble class I MHC (sHLA). To our knowledge, sHLA has not previously been shown to inhibit NK cytotoxicity, although the expression of class I HLA on the surface of TC has been shown to inhibit NK cytotoxicity. To study further the effect of sHLA on cell-mediated cytotoxicity, we added various concentrations of sHLA to EC mediating NK, ADCC, and CTL activities. All were inhibited in a dose-dependent manner. Taken together, these results demonstrate that (i) although fresh HUCB-NK are functionally immature in that they fail to lyse TC, they acquire lytic potential only with IL-2 and IL12; (ii) the increase in lytic potential is accompanied by an increase in the level of three lyric moieties known to mediate cytotoxicity, perforin, granzyme A, and granzyme B; (iii) the presence of sHLA class I in the serum of HUCB may be partially responsible for the lack of NK lytic activity.

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